GEOFFREY R. HOWE, PH.D. - TRIP REPORT

Lyon, Paris and Kiev
March 16, 1999 - March 26, 1999

Introduction:

The trip involved four meetings. The first took place in Lyon at the IARC from March 16 to March 17, 1999, and was a joint meeting of dosimetrists and epidemiologists involved in the studies of leukemia amongst liquidators in Belarus, Russia and Ukraine. The second was in Paris from March 18 to March 19, 1999 and was a joint meeting with the French representatives from IPSN to discuss the status of the Phase I study of leukemia, and the possibility of a Phase II study. The third meeting took place in Kiev from March 22 to March 25, 1999 and was concerned with the leukemia study, and the fourth, also in Kiev from March 25 to March 26, 1999, concerned the Ukrainian thyroid cancer study. Each meeting is discussed separately.

① **Dosimetry Meeting, Lyon:**

A number of items were discussed at the meeting and are documented in the minutes of the meeting prepared by Drs. Bouville and Chumak. The primary objective of the meeting was to give Dr. V. Krioutchkov an opportunity to present the SEAD method for assessing doses which he had developed under contract from Columbia University. Dr. Krioutchkov has written a detailed instruction manual, and prepared the necessary software to enable the method to be used. Prior to the meeting, he had spent some time in Washington to present his method to Drs. Bouville and Luckyanov and to prepare a possible manuscript for publication. His visit was interrupted by the very unfortunate death of his mother which meant that he was unable to complete his work in Washington.

During the Lyon meeting, Dr. Krioutchkov presented his method in some detail. It is based on the so-called IARC questionnaire designed by the same working group. Essentially, the method

identifies the fairly small number of critical factors which determine the dose which the particular liquidator had in relation to other liquidators in the same job group. Fuzzy set estimates are used to provide a region in which his dose is most likely to fall, and also sets an uncertainty on that range. Preliminary tests of the method have given good correlations with the recorded doses amongst professional radiation workers in the Obninsk registry.

The key feature, from my point of view, was the plan for implementing and testing the dose estimation procedure. In the context of the epidemiologic study it appears essential that the same dose estimation method should be applied to all cases and controls over the wide range of doses experienced. The questionnaire approach appears to be the only method which fulfills this criterion. Thus, the SEAD method could be used as a general method and be calibrated against a "gold standard" in order that adjustment for measurement error and dosimetry can be made in the epidemiologic study. Threet components are involved in the planned work over the next three to six months. The first will be some minor modifications and improvements to the SEAD method by Dr. Krioutchkov; the second will be a test based on 50 liquidators in Ukraine who have EPR measurements (regarded as the "gold standard") and cover a wide range of doses. The IARC questionnaire will be administered to the liquidators and then the SEAD method will be applied to the questionnaires and the results compared with the EPR dose estimates. In addition, the questionnaires will be subject to a more detailed and rigorous dose assessment procedure and these results, too, will be compared to the EPR dose estimates. The third component is a simulation study of the effect of differential measurement error by dose upon risk estimates, i.e., whether errors at low doses are less important on a proportionate scale than errors at high doses. I have promised to carry out this work and make the results available at the next planned meeting of dosimetrists which is planned for July of this year.

② **Meeting with Institut de Protection et Surete Nucleaires (IPSN) Collaborators, Paris:**
This meeting was mainly a review of what had been achieved in Phase I of the leukemia study and a discussion of the French interest in a possible Phase II study. Nothing really new emerged from

this meeting and Drs. Hubert and Tirmarche have promised to let us have their thoughts in writing as to where their interests might be if a Phase II study comes to fruition.

③ **Leukemia Meeting, Kiev:**

This involved a series of meetings in both plenary sessions and small group meetings. The main points which emerged from the various discussions are as follows:

A) Data for the cohort have now been obtained from the Chernobyl State Registry. The selection criteria were male and resident in one of the six oblasts originally chosen for the study at the time of registration. The total number of records is 100,058. Some tabulations of the data have been produced and are given in the latest quarterly report. I discussed some further tabulations with Drs. Gudzenko and Gubina and they agreed to run these tabulations. These mainly relate to missing identification data on the various records.

B) Primarily as a result of the pathology review, it is proposed to drop two of the original oblasts, namely, Sumska and Donetska because clinical records were lost due to a fire in the former case and a flood in the latter case. Thus, clinical records for retrospective leukemia cases could not in general be obtained for these two oblasts. The proposal is to replace these oblasts with Chernihivska and Poltavska. Visits are planned to both oblasts in the near future in order to assess the quality of data and the degree of cooperation likely to be encountered. This seems to be an acceptable proposal.

C) Some clarifications were obtained regarding the origins of the Chernobyl State Registry. Dr. Gudzenko stated that the original registry had been formed from government lists of liquidators sent to participate in the Chernobyl cleanup. Though some later registrations may have come from individuals when they received medical examinations, apparently the great majority were from the original lists. The State Registry is formed by taking computerized lists made at the oblast level. Thus, the concern over possible bias if the Registry was based purely on those medically examined is somewhat allayed by this information.

D) Some concerns were raised about the use and completeness of the National Cancer Registry. For example, the Registry has only recorded 2,000 leukemia cases in Dnipropetrovsk since 1991, yet in the oblast of Cherkasska which is about ten times smaller, 1,000 cases have been registered during the corresponding time period. The Cherkasska oblast has its own special registration system and does not appear to contribute to the National Registry. The problem probably arises because leukemia cases diagnosed in hematological departments are not always notified to the local dispensary which is the basis for the National Registry. This reinforces the need to establish special registries for hematologic cases if the Phase II study goes ahead.

It also appears that there may be political difficulties in working with the National Registry. I promised to visit the Registry during my next visit in May to try to smooth out some of these problems, since I have reasonably good relationships with Drs. Federenko and Gulak who, of course, run the Registry.

E) Another issue which relates to the National Registry is the fact that they are developing computerized probabilistic record linkage systems themselves. The programmer who is doing this attended my workshop last December, but apparently the European Union, through Dr. Hans Storm, is planning to provide some resources for him to further develop this work. It would, of course, be logical and cost effective if we were to work in conjunction with the Registry to produce a unified record linkage system. I, therefore, have promised to discuss this issue when I visit the Cancer Registry in May this year, and to contact Hans Storm before I do so in order to achieve some degree of consistency and collaboration.

F) Dr. Gudzenko showed me some results of her recent analysis of leukemia occurring amongst liquidators to date. Case ascertainment is likely to be somewhat incomplete and, of course, no doses are available for analysis. Her original analysis compared observed rates to expected rates based on population data. This was not a particularly appropriate analysis, and she has now replaced it with a comparison of liquidators starting in 1986, liquidators starting in 1987 and

liquidators starting later. I promised to keep the results confidential but suffice it to say that the results are of considerable interest, particularly in the time dependency of the risks observed. I showed Dr. Gudzenko how to improve on the analysis using Poisson regression and offered to run her data through a more detailed analysis if she would send me the original data. She is willing to do so, but has to obtain permission from Dr. Ledoschuk and it is not clear if such permission is forthcoming. Nevertheless, her results do offer some support for approaching a Phase II study.

G) The results of the pilot study in Dnipropetrovsk were assessed in detail. These have been presented in the various quarterly reports but, overall, appear to be very encouraging with a relatively small lost to follow-up (about 10%). The latest investigation of lost to follow-up suggests that about half of those who were lost may be easily found leading to an overall loss of about 5% over a three-year period. The interviewing appears to have been relatively successful with approximately 35 interviews having been conducted based on 50 invitations to participate, i.e., a response rate of about 70%. This might be improved if facilities for local interviewing were provided. Apparently no one has refused the blood draw and Dr. Finch was satisfied with the procedures used for shipping blood back to Kiev. Of course, the shipping procedure will, to some extent, be dependent on the distance of the particular oblast from Kiev, and the transport available.

H) Discussions were held between the hematologists and the epidemiologists. It was pointed out that the original diagnoses were usually very good when bone marrow slides and peripheral blood smears were available. It is, therefore, a reasonable assumption that if the clinical record states that such biological material was available when the original diagnosis was made, but the material itself is now missing, it may be reasonable to accept the original diagnosis. The problem will arise when the clinical record does not state such biological material was used in the original diagnosis or where the clinical record is missing. Thus, the critical percentage is that of cases belonging to the latter two groups. This will be computed based on the data obtained

from the pathology review. In addition, the possibility that liquidators who have developed leukemia may have their biological material preferentially preserved needs to be investigated and this is planned for all oblasts intended to be included in the Phase II study if this comes to fruition.

I) Specific details of the procedures which would be used in the Phase II study for field work were considered. A number of specific questions were discussed, e.g., who should the interviewers be, where should the interviews be conducted, etc. and a complete list of such items was provided to Dr. Gudzenko. She has promised to address each of the specific questions before the next meeting in June so that the procedures can be incorporated into a detailed proposal for Phase II. We emphasized that it was essential that the procedures be described in detail and not in vague terms and Dr. Gudzenko appreciated the need for this.

J. I requested a summary by oblast for each of those intended to be included in the Phase II study of the important details for the study such, for example, who will be responsible at the oblast level for cooperation. Again, Dr. Gudzenko promised this summary and will send it to us prior to the June meeting.

K. Data management procedures as yet have not been designed and implemented. If the problems seen in the thyroid study in Kiev are to be avoided, and if the Phase II study happens, it will be essential that high priority be given to data management and processing during the early phases of such a study.

L) I promised to provide some modifications to the record linkage program so that internal linkages, ie. to identify duplicates within the same file, can be achieved.

M) At the last plenary session I emphasized strongly that the Phase II study would have essentially

two objectives: namely, to a) estimate risk of leukemia (and possibly lymphoma) as a function of dose; and b) to store biological samples for future processing. Thus, the study was emphasized to be an epidemiologic study. I pointed that "add ons," e.g., peripheral studies of treatment in the proposal could only be negative for the prospect of obtaining funding. Although this position is not popular with some of the scientists, Dr. Romanenko supported this position most strongly. I agreed that as I was drafting an outline for a possible Phase II proposal, I would return to Kiev for a week probably after the June meeting in order to start fleshing out such a proposal in collaboration with our Ukrainian colleagues. This, too, was strongly endorsed by Dr. Romanenko.

The other major issue considered at the last plenary session was the preparation of the report of the Phase I study. I stressed that there were two objectives for this report: a) to report back to the funding agencies which supported the Phase I study that they had "had their money's worth;" and b) (and possibly more importantly) the report should be a powerful tool for supporting a proposal for Phase II if this goes ahead. The list of consolidated tasks will be useful in preparing a first draft of the report, and Dr. Finch and I agreed to comment on such a draft which should be sent to us within a month or two. However, the final draft will have to be a much more readable document and should be understandable by those who have had little involvement in the study to date. This will be essential, for example, for reviewers of a Phase II proposal to appreciate the report and its implications for any future studies. Again, our Ukrainian colleagues seemed to enthusiastically endorse this approach.

N. In summary, I was encouraged by the visit to discuss the leukemia study. The Ukrainians seem to have a relatively good understanding of the scientific methodology involved and, in general, the results obtained from their various pilot studies and investigations have been encouraging. The analyses reported by Dr. Gudzenko should serve to support the rationale for a Phase II study. Although a final decision of whether to proceed with a Phase II proposal will, obviously, not be made until later in the year, the signs at the moment I feel are quite encouraging.

④ **Thyroid Meeting, Kiev:**

This involved meetings with Dr. Lichtarev's group, and primarily with DCC and epidemiology personnel at the Endocrinology Institute. The main points were as follows:

A) Dr. Lichtarev's group has promised to provide me with detailed dose distributions, and means and standard deviations for log (doses) by age group at exposure and gender by the time I return in May. This is essential for recalculating the power estimates more exactly.

B) Since Dr. Lichtarev is very keen on pursuing some risk analyses as soon as possible, I suggested he might look on a case-control basis or case-cohort basis at cases of thyroid cancer detected ***out*** of the screening study. The doses for the subjects could be those which his group has refined from the original true doses. I emphasized that the retrospective cases had to be treated separately from those enrolled in the screening study for obvious reasons. I also emphasized that interpreting results of such a study would be extremely difficult since the role of screening could not be addressed. This, too, was apparently recognized by the group. I offered to help them with such an analysis and this, too, was agreed to. Dr. Lichtarev, himself, was ill and unable to attend the meetings but he spoke with me by phone and seemed very enthusiastic and cooperative. The group will provide a brief protocol for such a study before they initiate it and I will review the protocol.

C) Some problems the group have encountered with probabilistic record linkage were discussed. The problems appear to be minor and reflect the fact that the individual carrying out the linkage was not the person who attended the workshop.

D) The problem of multiple dose records was discussed. This, apparently, has not been addressed in the study so far, i.e., duplicate dose records have not been identified. Clearly, an internal record linkage is required and this should be done as soon as possible. The dosimetrists feel that it will also be necessary to try to resolve some of the duplicates at the time of interviewing the study subjects, e.g., from the knowledge of geographic locations, etc. They suggested taking the

dosimetric database into the field using two laptop computers so that the dose records for subjects would be available to them. This seems reasonable and would not cost much. I promised to look at the issue of linking the file in such a way that all records have listed any potential duplicates so that dosimetrists at time of interview could pull all the possible duplicates and resolve them. Clearly, this approach needs some further work before implementing.

E) Discussions were held at the DCC and with the epidemiologists in conjunction with Dr. Mitchell and Professor Burch. The issue of duplicate dose records was discussed and although the DCC staff is aware of these, nothing has been done to resolve this issue. Probably about ten percent of all dose records are duplicates.

F) The data management of the thyroid study is substantially in arrears. Approximately, 23 forms are potentially involved for each study subject and the data entry programs have only been written for four of these forms. In terms of the data entry itself, about 2,000 records of approximately 2,500 have been entered for the locator form, about 800 records have been entered for the tracing form (filled in by the local medical authorities) and very small numbers for the dynamics of interview form. This means that the study cannot be monitored in an on-going fashion to detect errors and problems or to monitor progress. This is a very serious problem and must be a high priority item for rectification.

Part of the problem seems to have arisen because the data entry program that has been written includes substantial validity and consistency checks and a record cannot enter the database if it fails one of these checks. Thus, the data entry system "grinds to a halt" for any error which has to be resolved on the spot. Clearly, this is inefficient and Dr. Mitchell and I suggested some alternative procedures, i.e., no checks at time of data entry, but checks to be made on a batch processing basis and then resolved. Also, little thought has, as yet, been given to reports which should be generated by a data management system. Dr.. Mitchell and Professor Burch subsequently suggested some of the types of reports which should be generated.

G) The 20,000 dose records selected for the initial sample may not have all the dose records relevant to a particular individual. The random selection was apparently based on records, not people. Thus, there will have to be subsequent processing in order to determine all appropriate dose records for any individual included in the original sample.

H) Because of a lack of data management, it is still not possible to accurately quantify tracing and response rates. Some information pertaining to these issues based on either hand calculations or approximations is included in Professor Burch's trip report. One interesting factor to emerge is that the response rate in the city of Kiev (about 80%) is much greater than the general response rate (about 50%). This strongly suggests that ready accessibility to a screening center is an important determinant of participation; in addition, telephone contact is much more readily available in the city of Kiev as compared with the other oblasts.

I) Dr. Tereschenko made it clear that the physical capacity of the one fixed center in Kiev and one mobile team was approximately 5,000 to 6,000 screenings per year. Thus, in a two-year cycle 10,000 to 12,000 subjects could be screened. Dr. Tereschenko pointed out that if additional study subjects were to be screened, additional resources will be required. An alternative might be to have a three-year cycle but this raises the problem of interval cases, and how they are detected, and the quality of data which would be available for such cases.

J) In terms of tracing addresses, four methods are currently being used. These are the local medical authorities, the computerized linkage to the Chernobyl State Registry, manual searches of the passport office records (maintained at the oblast level) and manual searches of the records maintained by the so-called Chernobyl Department, again, at the oblast level. It appears as though the passport office and the Chernobyl Department may be a useful supplementary source for increasing the rate of locating addresses. This has not yet been fully pursued, but some work has been done. For example, in Ivankiv raion, Dr. Dereyenko found 229 addresses from 418 individuals who were missing addresses and 157 of these were still resident in the raion.

K) I raised the possibility of a joint analysis of data with that from Belarus and this was very enthusiastically received by Dr. Tronko and his colleagues. They suggested that a meeting between the two groups would be in order and I feel this worth considering. It may have some practical benefits, e.g., sharing ideas and methods but, in particular, would serve to better identify the two studies as essentially being two components of the same study.